# Temperature-Induced Crystallization and Compactibility of Spray Dried Composite Particles Composed of Amorphous Lactose and Various Types of Water-Soluble Polymer

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Received November 8, 1999; accepted December 23, 1999

**The purpose of this study was to investigate the temperature-induced crystallization and the compactibility of the composite particles containing amorphous lactose and various types of polymers. The composite particles were prepared by spray-drying an aqueous solution of lactose and various types of gel forming water-soluble polymers at various formulating ratios.**

**The stabilizing effect of hydroxypropylcellulose (HPC) and polyvinyl pyrrolidone (PVP) on amorphous lactose in the composite particles was smaller than that of sodium alginate in comparing at the same formulating ratios. The difference in the stability of amorphous lactose in the composite particles was attributed to the difference in the glass transition temperature (Tg) of the composite particles caused by the polymers formulated. The tensile strength of compacted spray-dried composite particles containing the polymers was higher than commercial lactose for direct tabletting (DCL21). The tensile strength of the composite particles was increased with an increase in water content in the particles. The difference in compactibility of the composite particles containing the different amount of polymer and water could be explained by the difference in Tg of the particles.**

**Key words** amorphous lactose; temperature-induced crystallization; tablet tensile strength; glass transition temperature; composite particle; water soluble polymer

Various types of polymers have been investigated to be formulated in the controlled releasing tablet.[1,2] However, polymeric materials are unsuitable for tabletting unless they are agglomerates because of their elastic and poorly flowing properties. In a previous paper,[3] we demonstrated that the spray-dried (SD) composite particles of a polymer with lactose possessed both a good compacting and controlled releasing property when used as a base of matrix tablets.

Lactose is a suitable material for combining with the polymeric materials, because it is widely used in tablet formulations due to its stable physical properties even in hygroscopic conditions. Spray-dried lactose is the first product specially designed for direct tabletting.[4] It has been reported that the compactibility of commercial spray-dried lactose was affected by the amount of amorphous lactose in the particles as well as the primary particle.[5] However, the amorphous lactose in the spray-dried particles is physically and thermally unstable.[6] Several workers have used amorphous lactose as an amorphous model substance. Stubberud *et al*. showed the effect of physically mixing polyvinyl pyrrolidone (PVP) with amorphous lactose on the crystallization of the amorphous lactose.[7] We have also reported that the temperature-induced and moisture-induced crystallization of amorphous lactose in a SD composite particle of lactose and sodium alginate was considerably depressed by the presence of the polymer in the particle.[8] The compaction properties of the composite particles with sodium alginate were found to be dependent on the sodium alginate content in the composite particle.[9]

The purpose of this paper was to investigate the effect of the types of polymers formulated to the composite particles on their thermo- and mechanophysical properties. The composite particles were prepared by spray drying solutions containing lactose and various types of gel-forming water soluble polymers. The temperature-induced crystallization of lactose in the composite particles and the compactibility of the composite particles were evaluated.

## Experimental

**Materials** Lactose (Pharmatose 450M, hereinafter-called Pharm. 450M) supplied from DMV, Netherlands was used as a base of direct tabletting filler. Sodium alginate (NSPLL), hydroxypropyl-cellulose (HPC-M) and PVP (Kollidon K90) were obtained from Kibun Food Chemifa, Japan, Nihonsouda, Japan and BASF, Germany, respectively. Commercial roller-dried $\beta$-lactose anhydrate (DCL21, DMV) was used as a reference of direct tabletting fillers.

**Preparation of Spray-Dried Composite Particles** In preparation for SD composite particles, mixtures of lactose (Pharm. 450M) and various types of water-soluble polymers were completely dissolved at various formulating ratios in 3000 ml of distilled water. The aqueous solution was spray-dried using a rotary atomizing spray-dryer (Type L-12, Ohkawara Kakoki, Japan).[3] The resultant SD composite particles were more spherical with smoother surface than the original crystalline lactose (Pharm. 450M) and commercial lactose for direct tabletting (DCL21). Regardless of the types of water-soluble polymer in the SD composite particles, the amorphous state of lactose in the particles was verified by a halo pattern in powder X-ray diffraction analysis (RAD-1C, Rigaku, Japan).

**Temperature-Induced Crystallization Studies** Temperature-induced crystallization of amorphous lactose in SD composite particles was measured with a differential scanning calorimeter (DSC 6200, Seiko Instrument Inc., Japan). The powder samples were dried in a vacuum oven at 80 °C (2 weeks) to remove the water from the samples (water content of samples: $<0.1\%$) (10). Each sample (10 mg) was placed in the non-hermetically sealed aluminum sample pans, and scanned at a heating rate of 10 °C/min.

**Measurement of Glass Transition Temperature (Tg)** To observe the glass transition of amorphous lactose, DSC analysis was performed at the heating rate of 20 °C/min in aluminum sample pans. To dry the sample and cancel the effect of the thermal history of each formulation before measurement of glass transition temperature (Tg), all amorphous mixtures were heated in the pans to about 150 °C and then cooled down to −50 °C by a liquid nitrogen cooling accessory at 20 °C/min. The Tg was calculated by using the half extrapolated heat capacity method.

**Evaluation of Compactibility** The compactibility of SD composite particles was evaluated by means of tensile strength of the compacts. Compaction of SD composite particles was carried out using an Inston-type hydraulic press (Autograph AG 5000D, Shimadzu Co., Japan). The weighed sample (200 mg) was compacted at a compressing velocity of 10 mm/min under the compression pressure (100, 200 and 400 MPa) using a die with an 8.0 mm internal diameter and flat-faced punches. The compacts were diametrically compressed at a velocity of 0.5 mm/min using an Instron-type hydraulic press (Autograph AG 500D, Shimadzu Co., Japan) to measure the

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tablet crushing strength, which is force required to fracture the compacts. The tablet tensile strength (Ts) required to split the compressed tablets was calculated by the following equation[11]:

$$Ts=\frac{2F}{\pi DT} \quad (1)$$

where $F$ (N) is the crushing force, $D$ (m) and $T$ (m) are the diameter and thickness of the compacts, respectively.

To observe the change in shape of the SD composite particles after tabletting, micrographs of the upper surface of tablets with SD composite particles were taken using a scanning electron microscope (JSM-T330, Nihon Denshi, Japan) at an accelerating voltage of 15 kV. Compacts prepared with 200 mg of particles at a compression pressure of 400 MPa were attached directly on the stage of the scanning electron microscope using a double-sided adhesive tape.

## Results and Discussion

**Stabilization of Amorphous Lactose in SD Composite Particles** As reported in the previous paper,[8] the DSC thermographs of SD composite particles consisting of amorphous lactose and sodium alginate showed no exothermic peak at around 170 °C ascribed to transformation of amorphous to crystalline form of lactose, suggesting thermal stabilization of amorphous lactose in the composite particles with sodium alginate. To clarify the thermally stabilizing effect of the type of polymers on the crystallization of amorphous lactose in SD composite particles, different SD composite particles containing various types of water-soluble polymers such as HPC and PVP were prepared. The DSC analysis showed that the incorporation of the polymers into the SD composite particles led to a decrease in the exothermic peak areas at a temperature of around 170 °C, which represented the transformation of amorphous lactose to crystalline form (Fig. 1). Considering the area of an exothermic peak in DSC curves, the stabilizing effect of HPC and PVP was lower than sodium alginate.

In measuring the Tg of the dried SD composite particles with the polymers (water content: $<0.1\%$), the values increased with increasing polymer content. The SD composite particles containing the sodium alginate showed a higher Tg than those with other polymers, HPC and PVP, at every formulating ratio of polymer (Fig. 2). The lines in Fig. 2 are depicted based on the Gordon Taylor equation[12,13]:

$$Tg_{mix}=\frac{w_1Tg_1+Kw_2Tg_2}{w_1+Kw_2} \quad (2)$$

where $Tg_{mix}$, $Tg_1$ and $Tg_2$ are the Tg of the mixture, polymer and amorphous lactose, respectively, and $w_1$ and $w_2$ are the weight fractions of polymers and lactose, respectively. $K$ is a constant defined by the following equation:

$$K=\frac{\rho_1Tg_1}{\rho_2Tg_2} \quad (3)$$

where $\rho_1$ and $\rho_2$ are the density of polymer and amorphous material. Considering the Tg of original polymers (sodium alginate: 152±2 °C, HPC: 156±2 °C, and PVP: 176±1 °C), it was expected that the Tg of the composite particles with PVP was higher than that with sodium alginate and HPC. However, the measured Tg values of the composite particles containing sodium alginate were much higher than its theoretical line predicted by the Gordon–Taylor equation (Eq. 2).

Zografi and co-workers have reported a similar specific interaction which affected the Tg values for an amorphous mixture of indomethacin and PVP.[13] In this case, hydrogen bonds between the carboxyl group and the carbonyl group may play an important role in those interactions. The smaller change in Tg of the composite particles with HPC and PVP in increasing the polymer contents could explain the lesser thermal stability of the composite particles containing the sodium alginate.

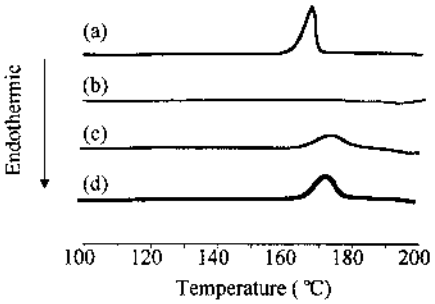


Fig. 1. DSC Thermographs of SD Composite Particles Containing Various Types of Water-Soluble Polymer

(a) None (100% amorphous lactose), (b) sodium alginate (NaAlg), (c) HPC, (d) PVP. Polymer content in SD composite particles: 10%.

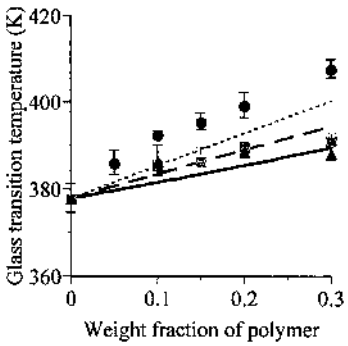


Fig. 2. Glass Transition Temperature (Tg) of SD Composite Particles (SDCP) with Various Types of Water-Soluble Polymer

(●) Sodium alginate, (▲) HPC, (■) PVP. The data are the average values of three runs. The lines show the predicted values from the Gordon Taylor equations; (——): SDCP with sodium alginate, (------): SDCP with HPC and (– – –) : SDCP with PVP.

**Compactibility of SD Composite Particles** The compactibility of SD composite particles was evaluated by comparing the tensile strength of tablets prepared with the composite particles containing the various types of polymers (Table 1). While the compactibility of SD composite particles with sodium alginate was markedly reduced when the sodium alginate content was higher than 20% in SD composite particles, the compactibility of the SD composite particles containing HPC and PVP was comparable to that of the SD amorphous lactose regardless of the polymer content.

To clarify the effect of the polymer type in the SD composite particles on the tablet tensile strength, the microstructure of tablets prepared with the SD composite particles was observed with scanning electron micrographs. The micrographs of the upper surface of the tablets are shown in Fig. 3. When the SD composite particles containing 30% of HPC or PVP were tabletted, a smooth surface of tablet was observed as well as those containing 10% of sodium alginate, suggesting occurrence of the fusion and cohesion of the SD composite particles during compression. These photographic observations clearly explain the difference in tensile strength of

these tablets.

To confirm the factors controlling the fusing and cohering properties of the particles, the effect of the moisture content in SD composite particles containing various formulating ratios of sodium alginate on their tensile strength was evaluated (Table 2). It is well known that the Tg values decrease with increasing the water content of lactose.[14] Irrespective of the sodium alginate content in the particles, the Tg values decreased as expected (Table 2). The tensile strength of tablet with SD composite particles containing 10% of sodium alginate was increased with increasing water content. The micrographs of the upper surface of the tablets with the SD composite particles revealed that the fusing and cohering property of the composite particles decreased with a decrease in water content in the composite particles (Fig. 4). The change in fusing property of the particles during compression can be explained by the change in the Tg of the composite particles (Table 2). However, the tensile strength of tablet prepared with the SD composite particles containing 30% sodium alginate was quite low even at the higher water content, although the particles having 6.3 or 8.8% water content possessed a low enough Tg to be fused. Based on these results, the compaction properties of the composite particles could be attributed to both the glass transition temperature of the composite particles and the bonding characteristics of the original polymers on the surface of composite particles.

Table 1. Tensile Strength of SD Composite Particles with Various Types of Water-Soluble Polymer: Sodium Alginate, HPC and PVP

| Sample | | Tensile strength (MPa) | | | |
|---|---|---|---|---|---|
| Polymer | Content | (C.P) | 10 MPa | 200 MPa | 400 MPa |
| NaAlg | 10 | | 2.1 (0.1) | 3.4 (0.1) | 7.3 (0.7)[b] |
| | 20 | | N.C.[a] | 1.1 (0.1) | 1.8 (0.3) |
| | 30 | | N.C | N.C | 0.7 (0.1) |
| HPC | 10 | | 1.8 (0.3) | 3.1 (0.2) | 7.0 (0.4) |
| | 20 | | 2.3 (0.1) | 4.2 (0.3) | 6.3 (0.5) |
| | 30 | | 2.1 (0.2) | 3.5 (0.3) | 6.4 (0.5) |
| PVP | 10 | | 2.4 (0.2) | 5.5 (0.1) | 7.2 (1.2) |
| | 20 | | 3.0 (0.3) | 6.4 (0.9) | 8.0 (1.0) |
| | 30 | | 2.6 (0.3) | 5.2 (0.2) | 9.0 (0.6) |
| 100% amorphous lactose | | | | 2.4 (0.1) | 4.0 (0.2) |
| 7.4 (0.6) | | | | | |
| DCL21 | | | 0.7 (0.1) | 1.7 (0.0) | 3.7 (0.1) |

*a*) N.C.: No compacts were obtained. *b*) The numbers in parenthesis represent the standard deviation.

Effect of polymer content in SD composite particles on the tensile strength of their tablet. Each data represents the mean±S.D. for four determinations.

Table 2. Effect of Water Content in SD Composite Particles (SDCP) on the Tensile Strength of Their Tablet and Glass Transition Temperature of the Particles

| Content in SDCP | | Tensile strength (MPa) | Glass transition temp. (K) |
|---|---|---|---|
| NaAlg (%) | Water (%) | | |
| 0 | 0 | 2.7 (1.0) | 378.0 (3.3)[b] |
| | 2.6 | 5.0 (0.5) | 352.6 (2.7) |
| | 3.6 | 5.2 (0.4) | 341.3 (2.9) |
| | 5.2 | 5.5 (0.6) | 323.7 (0.9) |
| 10 | 0 | 0.7 (0.1) | 392.6 (0.8) |
| | 2.6 | 2.9 (0.4) | 366.1 (3.6) |
| | 4 | 4.8 (1.1) | 357.1 (1.8) |
| | 5.6 | 6.5 (0.2) | 337.6 (5.1) |
| 30 | 0 | N.C.[a] | 407.7 (1.9) |
| | 3.6 | N.C | 363.9 (2.1) |
| | 4.1 | N.C | 360.8 (0.9) |
| | 6.3 | 0.3 (0.0) | 346.4 (1.6) |
| | 8.8 | 1.6 (0.1) | 340.1 (1.2) |

*a*) N.C.: No compacts were obtained. *b*) The numbers in parenthesis represent the standard deviation.

Each data represents the mean±S.D. for four or three determinations.

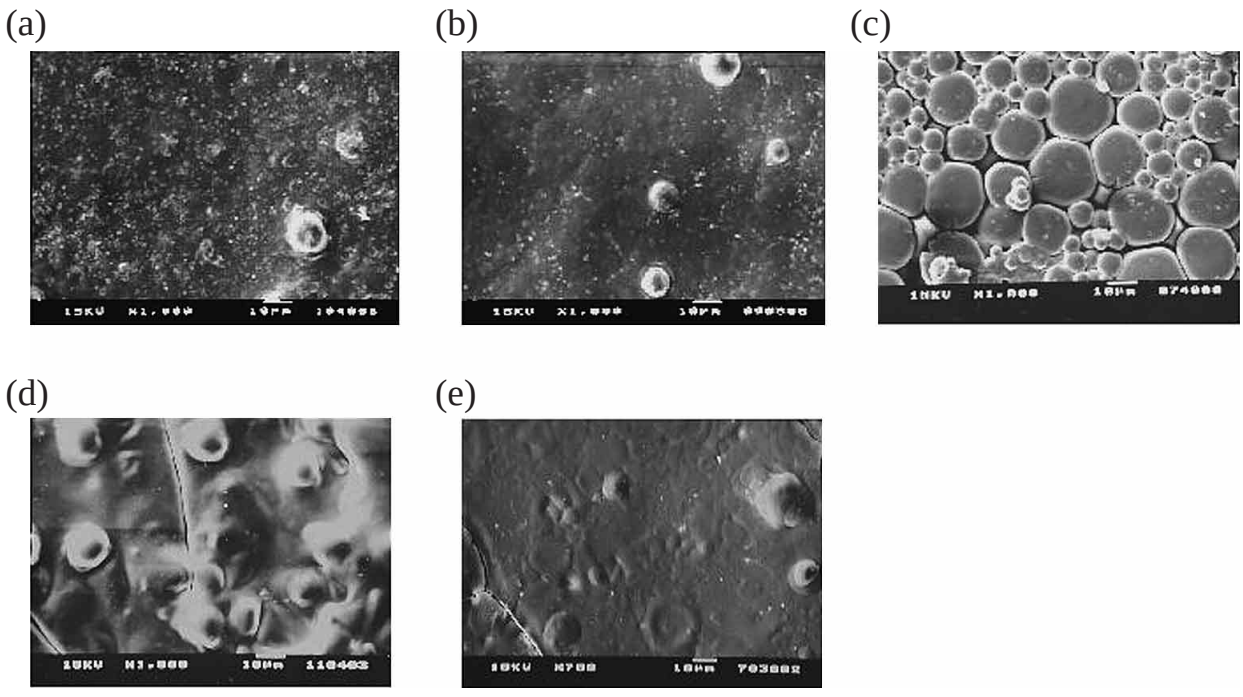


Fig. 3. Scanning Electron Micrographs of the Upper Surface of Tablets Compacted at Compression Pressure of 400 MPa

(a) 100% amorphous lactose, (b) SD composite particles (SDCP) with 10% sodium alginate, (c) SDCP with 30% sodium alginate, (d) SDCP with 30% HPC, (e) SDCP with 30% PVP.

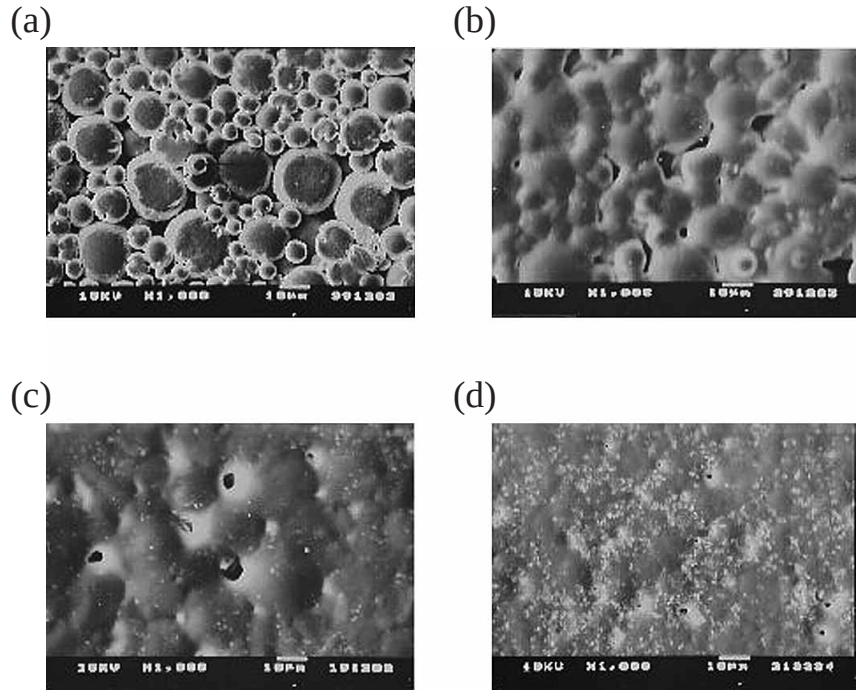


Fig. 4. Scanning Electron Micrographs of the Upper Surface of Tablets Containing SD Composite Particles Containing 10% Sodium Alginate with Various Water Contents

(a) 0 %, (b) 2.6%, (c) 4.0 %, (d) 5.6 %.

## Conclusions

The SD composite particles of lactose and water-soluble polymers (sodium alginate, HPC and PVP) possessed different properties depending on the type of the polymers. The temperature-induced crystallization of amorphous lactose in the particles was most depressed by formulating sodium alginate, which may have a specific interaction with lactose. Tabletting property of the SD composite particles containing HPC or PVP was almost independent of the formulating ratios, while this property was significantly decreased by formulating sodium alginate into the particles.

**Acknowledgements** The authors are grateful to Miss S. Inoue, Mr. T. Yasuda and Mr. S. Nagira for their technical assistance in part of this work.

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